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Endoscopic resection versus radical gastrectomy for early gastric cancer in Asia: A meta-analysis**Fei-Long Ning^{a, b, c, #}, Chun-Dong Zhang^{a, #}, Peng Wang^a, Shuai Shao^a, Dong-Qiu Dai^{a, d, e, *}**[#]Contributed equally.^a Department of Gastrointestinal Surgery, the Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning, China.^b Department of General Surgery, Xuzhou Hospital of Traditional Chinese Medicine, Xuzhou, Jiangsu, China.^c Department of General Surgery, Affiliated Xuzhou Hospital of Nanjing University of Chinese Medicine, Xuzhou, Jiangsu, China.^d Cancer Research Institute, China Medical University, Shenyang, Liaoning, China.^e Cancer Center, the Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning, China.

*Corresponding author. Department of Gastrointestinal Surgery and Cancer Center, the Fourth Affiliated Hospital of China Medical University & Cancer Research Institute of China Medical University, Shenyang 110032, Liaoning, China. *E-mail address:* daidq63@126.com or cmudaiddq@126.com (D.Q. Dai).

Telephone: +86-24-62043110. *Fax:* +86-24-62043110.

Running title: Endoscopic resection versus radical gastrectomy for early gastric cancer

ABSTRACT

Background: To compare the efficacy and safety of endoscopic resection (ER) and radical gastrectomy (RG) for early gastric cancer (EGC) in Asia.

Materials and methods: We systematically searched relevant articles published before September 1, 2017. We evaluated the quality of the included non-randomized studies using the Newcastle-Ottawa Scale (NOS). Meta-analysis was carried out using RevMan 5.3 software. The odds ratio (OR) with 95% confidence intervals (CI) were used for the dichotomous data.

Results: Fifteen retrospective studies were included in this analysis (3737 patients in the ER group and 4246 patients in RG group). No significant differences in the three-year survival rate (OR, 0.87; 95%CI, 0.50–1.53) and five-year survival rate (OR, 0.81; 95%CI, 0.58–1.13) between the ER and RG groups were observed. Although patients undergoing ER had a higher risk of recurrence (OR, 6.07; 95%CI 4.17–8.84) and the occurrence of metachronous cancer (OR, 8.35; 95%CI, 5.48–12.75), recurrent or metachronous gastric cancers following ER were successfully detected and removed using the endoscopic technique. Higher recurrence in the ER group may be associated with its lower en bloc resection rate (OR, 0.05; 95%CI, 0.02–0.14) and complete resection rate (OR, 0.03; 95%CI, 0.01–0.08). Importantly, although the three-year survival and five-year survival were similar in the two groups, the complication rate in the ER group was significantly lower than that in the RG group.

Conclusion: ER is a good choice for patients with small EGC lesions (≤ 2 cm) without lymph node metastasis, especially in elderly patients with various medical comorbidities and in patients who cannot tolerate abdominal surgery or who meet the criteria but decline surgery. In contrast, RG is recommended when the diameter of the tumor is large (> 2 cm) and preoperative examination suggests the possible presence of lymph node metastasis.

Keywords: Early gastric cancer; Asia; Endoscopic resection; Radical gastrectomy; Meta-analysis

1. Introduction

Gastric cancer is one of the most significant diseases threatening public health. The morbidity and mortality associated with gastric cancer is decreasing; however, gastric cancer remains one of the most common malignant tumors globally with morbidity ranked fifth and mortality ranked second worldwide [1, 2]. Due to the development of endoscopic devices and improvements in diagnostic technologies, the detection rate of early gastric cancer (EGC) has increased [3].

The standard treatment for curing EGC is tumor resection with lymph node dissection, which is also referred to as radical gastrectomy (RG) [4]. Patients who have undergone RG tend to have a favorable prognosis, but with comparatively greater damage, inferior quality of life and slow recovery [5, 6]. Recently, endoscopic resection (ER) has been used in Japan and is now a common surgical technique. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). This technique is mainly used for EGC without lymph node metastasis [7, 8]. ER, a less invasive technique with fewer costs, can reduce surgical risks in patients and improve the quality of life [8, 9]. Several studies have compared ER and gastrectomy for EGC [10–24]; however, the results were inconsistent. Treatment methods for patients with gastric cancer vary in Japan and Western countries due to differences in diagnostic criteria [25]. In addition, the difficulty and complexity of the surgical procedure may be increased due to the weight index difference between Western and Eastern patients. Thus, given these differences, a systematic review and meta-analysis was carried out, specifically focusing on Asian patients, to determine the advantages and disadvantages of both techniques in the treatment of EGC.

2. Materials and methods

2.1. Search strategy

We systematically searched PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Web of Science databases for relevant articles published before September 1, 2017. The following subject terms were used to carry out the literature search: “early gastric cancer”, “endoscopic resection”, “endoscopic mucosal resection”, “endoscopic submucosal dissection” and “gastrectomy”. The bibliography of all retrieved articles was investigated in order to identify additional potentially relevant studies.

2.2. Inclusion criteria

The inclusion criteria were as follows: all studies comparing ER vs. RG for EGC; studies on Asian patients; studies analyzing the following endpoints: en bloc resection, complete resection, complications, recurrence, metachronous cancer, three-year survival, and five-year survival. Metachronous cancer was defined as new adenocarcinoma in different areas from the initial cancer occurring at least 1 year after the initial ESD or RG [26]. Local recurrence was defined as adenocarcinoma detected at the resection site at least 12 months after ESD or RG with two negative results in previous follow-up esophagogastroduodenoscopy [27].

2.3. *Exclusion criteria*

The exclusion criteria were as follows: guideline articles, comments, reviews; studies on other gastric lesions, such as: recurrent EGC and other gastrointestinal lesions, other than EGC; low-quality studies without adequate data relating to the required characteristics, such as: studies that obtained scores of < 5 were considered as low quality studies; only the most informative and most recent published articles were chosen, if the studies were carried out by the same authors.

2.4. *Data extraction and study quality assessment*

Two authors independently extracted the relevant data from the articles. The extracted data included the characteristics of the study, participants in each group, subject terms, and endpoints which were determined from the titles and abstracts, and full articles were obtained when necessary. The results were compared and the quality of the studies was evaluated. If there was disagreement, this was resolved by a third investigator. Quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS).

2.5. *Statistical analysis*

Meta-analysis was carried out using RevMan 5.3 software. The odds ratio (OR) with 95% confidence intervals (CI) were used for the dichotomous data. The chi-square test was used to assess heterogeneity in the study results. If the results were statistically homogeneous ($P > 0.1$, $I^2 \leq 50\%$), then the fixed-effects model was selected for meta-analysis. The random-effects model was used for meta-analysis when the study results were statistically heterogeneous ($P < 0.1$, $I^2 > 50\%$).

3. **Results**

Our search strategy yielded a total of 2355 articles (Figure 1). Duplicate articles (of which there were 712) were excluded after browsing the title; 1251 were excluded as they did not compare ER and RG and 369 were excluded because they were comments, case-reports or reviews. Of the remaining 23 articles, 8 were excluded: 2 due to enrolled patients having another type of cancer and 6 articles did not have the required endpoints. Of the remaining 15 studies, 12 were from Korea, 2 were from Japan, and 1 study was from China. These 15 studies [10–24] included a total of 7983 patients: 3737 in the ER group and 4246 in the RG group. All of the articles were full texts of retrospective case-control studies. The key characteristics and quality assessments of the studies are listed in Table 1. The clinical endpoints of ER compared to RG are shown in Table 2. Publication bias for the outcomes was determined by funnel plots (Fig. 9), and no publication bias was detected.

3.1. Recurrence

Twelve studies [11, 12, 14–18, 20–24] compared the recurrence. The results of these studies were statistically homogeneous ($P = 0.10$; $I^2 = 37\%$), thus a fixed-effects model was used. The meta-analysis revealed that the recurrence rate in the ER group (163/3565) was higher than that in the RG group (32/4143) (OR, 6.07; 95%CI 4.17–8.84; $P < 0.001$) (Fig. 2).

3.2. Metachronous cancer

Twelve studies [12, 14–24] compared the metachronous cancer. No heterogeneity was detected in the studies ($P = 0.95$; $I^2 = 0\%$), thus a fixed-effects model was used. Pooling the data revealed that metachronous cancer in the ER group (189/3558) was higher than that in the RG group (24/4112) (OR, 8.35; 95%CI, 5.48–12.75; $P < 0.001$) (Fig. 3).

3.3. En bloc resection

Eight studies [10, 11, 13–15, 17, 18, 22] reported the results of en bloc resection for ER vs RG. There was no heterogeneity among the studies ($P = 0.95$; $I^2 = 0\%$), thus a fixed-effects model was used. The analysis showed that the en bloc resection rate was lower in the ER group (825/915) than in the RG group (824/824) (OR, 0.05; 95%CI, 0.02–0.14; $P < 0.001$) (Fig. 4).

3.4. *Histological complete resection*

Nine studies [10, 11, 13–15, 17, 18, 21–22] reported the rate of histological complete resection for ER vs RG. There was no heterogeneity among the studies ($P = 0.89$; $I^2 = 0\%$), thus a fixed-effects model was used. The analysis showed a lower complete resection rate in the ER group (818/942) than in the RG group (968/968) (OR, 0.03; 95%CI, 0.01–0.08; $P < 0.001$) (Fig. 5).

3.5. *Number of patient deaths in three years*

In this meta-analysis, the number of patient deaths in three years was used to evaluate patient three-year survival. Five studies [10–13, 19] compared the number of EGC patients who died within three years in each group. Analysis demonstrated that there was no difference between the ER (28/352) and RG groups (32/493) in terms of the number of patients who died within three years (OR, 0.87; 95%CI, 0.50–1.53; $P = 0.64$) (Fig. 6). No heterogeneity was found ($P = 0.65$; $I^2 = 0\%$).

3.6. *Number of patient deaths in five years*

In this meta-analysis, the number of patient deaths in five years was used to evaluate patient five-year survival. Eight studies [11, 12, 16–20, 22, 24] provided the number of EGC patients who died within five years in each group. The pooled data showed that the number of patients who died within five years in the ER group (76/1482) and RG group (92/1649) was similar (OR, 0.81; 95%CI, 0.58–1.13; $P = 0.22$) (Fig. 7). No heterogeneity was found in the studies ($P = 0.99$; $I^2 = 0\%$).

3.7. *Complications*

Thirteen studies [11–13, 15–24] provided data on the complication rate following treatment of EGC. There was heterogeneity in these studies ($P < 0.0001$; $I^2 = 75\%$), thus a random-effects model was used. The results of these studies demonstrated that the general complication rate following RG (290/3653) was higher than that following ER (557/4001) (OR, 0.43; 95%CI, 0.30–0.63; $P < 0.001$) (Fig. 8).

4. **Discussion**

Several clinical studies have compared the outcome of ER and RG in patients with EGC. However, meta-analysis is better for evaluating the safety and efficacy of these treatments, compared with a single

clinical study. Furthermore, the treatment of patients with gastric cancer in Japan and Western countries varies due to differences in the diagnostic criteria used. A lesion that is diagnosed as non-invasive EGC according to Japanese guidelines only can be diagnosed as atypical hyperplasia or dysplasia using endoscopy in Western countries and patients may not receive any treatment [28]. In addition, the difficulty and complexity of the surgical procedure is different between patients in Asia and Western countries due to discrepancies in the weight index [25]. Thus, the aim of this meta-analysis was to assess the outcomes following ER and RG for EGC in Asian patients.

The data showed that recurrence and the occurrence of metachronous cancer following ER were higher than those following RG. It is possible that the comparatively lower en bloc resection rate and histological complete resection rate was related to higher recurrence. Tumors with a large diameter and deep infiltration may have increased the difficulty in achieving en bloc resection and complete resection in patients in the ER group. The statistical analysis showed that the en bloc resection rate and histological complete resection rate were lower in the ER group than in the RG group. Furthermore, EGC is defined as gastric cancer where tumor invasion is confined to the mucosa or submucosa regardless of lymph node involvement. A number of patients with EGC also have lymph node metastasis. The ER technique only resects the tumor without lymph node dissection, which may be closely linked with cancer recurrence. In this meta-analysis, some studies reported gastric recurrence rate in the ER and surgery groups of 0%-14% and 0%-1.7% [11, 12, 14–18, 20–24]. Moreover, the patient's entire stomach is preserved after ER while the patient's stomach is partly or not preserved after RG. Similar to most other gastric cancers, metachronous cancer generally occurs in the middle or lower part of the stomach [16, 29, 30]. The gastric mucosa of the preserved stomach tends to contain regions with a high possibility of gastric cancer development such as mucosa with intestinal metaplasia and severe glandular atrophy [31]. Patients with EGC, whose stomach is preserved after ER, have a high risk of subsequent gastric cancer and the rate of metachronous cancer has been recorded as 20% [32]. Furthermore, the incidence of metachronous cancer may also give rise to high recurrence [33].

The statistical analysis showed that there was no difference in the 3-year and 5-year survival rate between the ER group and the RG group despite high recurrence and the occurrence of metachronous cancer. Nevertheless, it is widely acknowledged that the main aim of cancer treatment and the most important indicator in evaluating the clinical efficacy and outcomes of cancer treatment is overall survival rate.

The similar overall survival rate in the ER and RG groups may be associated with the following factors: Firstly, the invasion depth of tumor (T staging) in EGC can be accurately evaluated. Accurate preoperative

evaluation or pretreatment T staging is essential to determine surgical planning. Currently, endoscopic ultrasonography (EUS) can provide accurate information on invasion depth, morphology and size of the tumor with high accuracy and is considered a standard for T staging of EGC [34, 35]. Secondly, preoperative assessment of lymph node involvement (N staging) in patients with EGC is also feasible. Although lymph node metastasis may occur in several patients with EGC, lymph node metastasis is comparatively rare in these patients. Only 2.2% of patients with EGC and mucosal invasion have regional lymph node metastases and 17.9% of patients with submucosal invasion have lymph node metastases [29]. At present, high-resolution CT, combined with EUS when necessary, can predict the involvement of lymph nodes and distant metastasis, and is considered a reliable N staging tool for preoperative assessment. ER is not recommended for patients with possible lymph nodes metastasis. Thirdly, the overall survival of patients following ER may not be affected as most metachronous cancer can be successfully detected and removed by endoscopic techniques in the early stages as reported in previous studies [36].

This meta-analysis also showed that there were statistically significant in the complication rate between the two groups. The complication rate in the ER group was lower than that in the RG group. The complication rate is closely associated with the patients' quality of life and long-term outcomes [37, 38]. In general, the recognized complications during or after ER are bleeding and perforation [9], even in the hands of experienced physicians, and these complications can be typically managed with endoscopy [39]. In comparison, RG often leads to comparatively greater damage and patients treated with RG are prone to complications compared to those treated with ER. Further interventions may be required for possible severe complications such as anastomotic leakage, intestinal obstruction and anastomosis site stricture [40, 41]. These may give rise to increased costs and long-term hospital stay. Thus, although ER failed to achieve adequate oncological clearance and may have a higher risk of metachronous cancer and cancer recurrence, it has not been shown to negatively influence long-term prognosis. The quality of life of patients undergoing ER was observed to be better with preservation of digestive function.

We suggest that an effective preoperative assessment should be carried out in Asian patients with EGC and reasonable and personalized treatment is proposed. A proper selection of patients is essential to improve the clinical outcomes of ER. Some studies indicated that ER can be considered as a therapy for EGC that is smaller than 3 cm in diameter [10, 15–16, 19, 21–23]. In other studies, ER of focal nodules (≤ 2 cm) can be safely performed in the setting of EGC [17, 18]. Notably, the Japanese gastric cancer guidelines recommend that ER should be considered for EGC lesions that ≤ 2 cm diameter [4]. In our institution, ER is recommended

as a therapy for EGC that is smaller than 2 cm in diameter.

In conclusion, ER is a good choice for patients with small EGC lesions (≤ 2 cm) without lymph node metastasis, especially in elderly patients with various medical comorbidities and in patients who cannot tolerate abdominal surgery or who meet the criteria but decline surgery. In contrast, RG is recommended when the diameter of the tumor is large (> 2 cm) and preoperative examination suggests the possible presence of lymph node metastasis. However, the studies included in this meta-analysis were retrospective observational studies, with a comparatively low quality and appreciable heterogeneity. More high-quality and larger prospective randomized, controlled trials are required for future meta-analyses. Our results require validation with high-quality, randomized, controlled trials.

Ethical approval

There is no need to gain Ethical Approval for this meta-analysis.

Conflict-of-interest statement

The authors have declared that there are no conflicts of interest.

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Tables and Figures legends

Tables legends

Table 1. Characteristics and NOS score of included studies in the meta-analysis.

Table 2. Clinical Endpoints Comparing ER and RG.

Figures legends

Fig. 1. Selection of studies for the meta-analysis.

Fig. 2. Forest plot of recurrence comparing ER and RG.

Fig. 3. Forest plot of metachronous cancer comparing ER and RG.

Fig. 4. Forest plot of en bloc resection comparing ER and RG.

Fig. 5. Forest plot of histologically complete resection comparing ER and RG.

Fig. 6. Forest plot of number of patients death in three years comparing ER and RG.

Fig. 7. Forest plot of number of patients death in five years comparing ER and RG.

Fig. 8. Forest plot of complication rate comparing ER and RG.

Fig. 9. Funnel plot of recurrence

Table 1. Characteristics and NOS score of included studies in the meta-analysis.

Study	Country	Patients (ER/RG)	Mean Age (yr) (ER/RG)	Type of ER	Type of RG	Endpoints	NOS score
Kim, 2000 ¹⁰	Korea	20/35	59.6/58.1	EMR	a	3, 4, 5	8
Etoh, 2005 ¹¹	Japan	49/44	82.2/84.2	EMR	a, b	1, 3, 4, 5, 6, 7	7
Choi, 2011 ¹²	Korea	172/379	59.3/58.4	EMR	a, b	1, 2, 5, 6, 7	8
Chiu, 2012 ¹³	China	74/40	66.3/67.0	ESD	a, b, c, d	3, 4, 5, 7	8
Chung, 2014 ¹⁴	Korea	76/149	61.1/56.7	ESD	NR	1, 2, 3, 4	6
Kim, 2014 ¹⁵	Korea	142/71	62.0/56.7	ESD	a, b, c, d	1, 2, 3, 4, 7	8
Park, 2014 ¹⁶	Korea	132/132	73.9/74.4	ESD	a, b	1, 2, 6, 7	7
Choi, 2015 ¹⁷	Korea	261/114	62.0/62.0	EMR, ESD	a, b, c, d	1, 2, 3, 4, 6, 7	7
Kim, 2015 ¹⁸	Korea	165/292	62.0/60.0	EMR, ESD	a, b, c, d	1, 2, 3, 4, 6, 7	8
Yamashina, 2015 ¹⁹	Japan	42/13	71.5/69.0	EMR, ESD	NR	2, 5, 6, 7	7
Pyo, 2016 ²⁰	Korea	1290/1273	61.0/59.0	EMR, ESD	a, b	1, 2, 6, 7	8
Ryu, 2016 ²¹	Korea	81/144	63.6/61.3	ESD	a, b	1, 2, 4, 7	7
Chang, 2017 ²²	Korea	74/79	65.0/63.0	ESD	a, b	1, 2, 3, 4, 6, 7	8
Hahn, 2017 ²³	Korea	817/1206	61.9/57.0	ESD	a, b, c, d	1, 2, 7	6
Jeon, 2017 ²⁴	Korea	342/275	62.9/57.7	ESD	a, b, c, d	1, 2, 6, 7	7

ER = endoscopic resection, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, RG = radical gastrectomy, NOS = Newcastle-Ottawa Scale, NR = not reported.

Endpoints: 1, recurrence; 2, metachronous cancer; 3, en bloc resection; 4, histologically complete resection; 5, three-year survival; 6, five-year survival; 7, complications.

a, radical subtotal gastrectomy; b, radical total gastrectomy; c, laparoscopic surgery; d, open surgery.

Table 2. Clinical Endpoints Comparing ER and RG.

Endpoints	No. Patients	No. Trials	ER	RG	OR (95% CI)	<i>P</i> Value	<i>I</i> ² , %	P Value for Heterogeneity
Recurrence	7708	12	163/3565	32/4143	6.07 (4.17, 8.84)	<0.001	37	0.10
Metachronous cancer	7670	12	189/3558	24/4112	8.35 (5.48, 12.75)	<0.001	0	0.95
En bloc resection	1739	8	825/915	824/824	0.05 (0.02, 0.14)	<0.001	0	0.95
Histologically complete resection	1910	9	818/942	968/968	0.03 (0.01, 0.08)	<0.001	0	0.89
Numbers of patient deaths in three years	845	5	28/352	32/493	0.87 (0.50, 1.53)	0.64	0	0.65
Numbers of patient deaths in five years	3131	8	76/1482	92/1649	0.81 (0.58, 1.13)	0.22	0	0.99
Complication	7654	13	290/3653	557/4001	0.43 (0.30, 0.63)	<0.001	75	<0.0001

ER = endoscopic resection, RG = radical gastrectomy, OR = odds ratio.

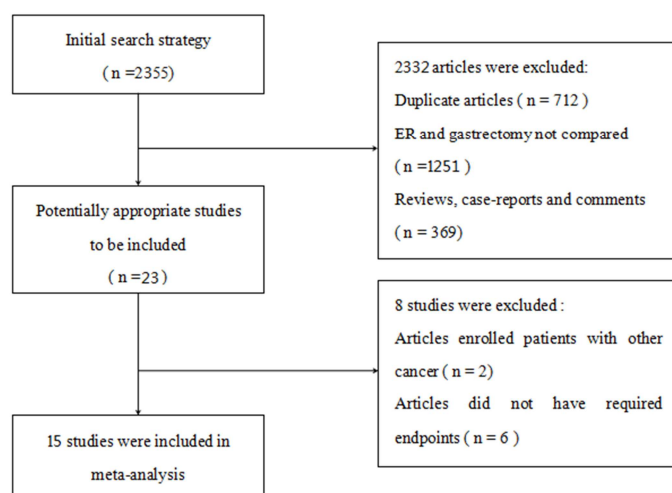
Fig. 1. Selection of studies for the meta-analysis.

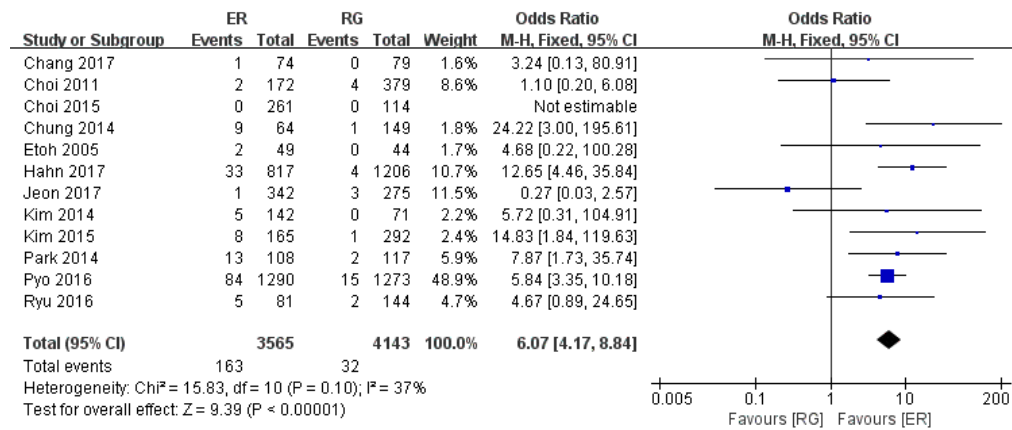
Fig. 2. Forest plot of recurrence following ER compared with RG.

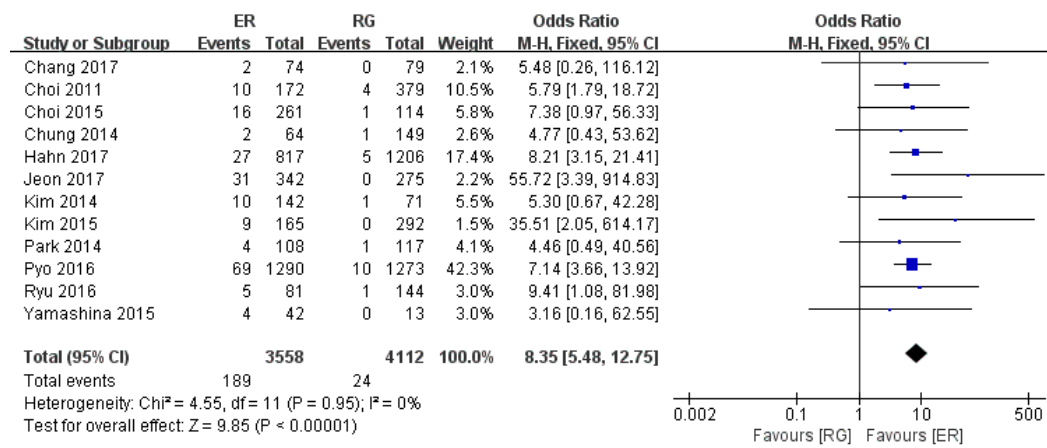
Fig. 3. Forest plot of metachronous cancer in the ER group compared with the RG group.

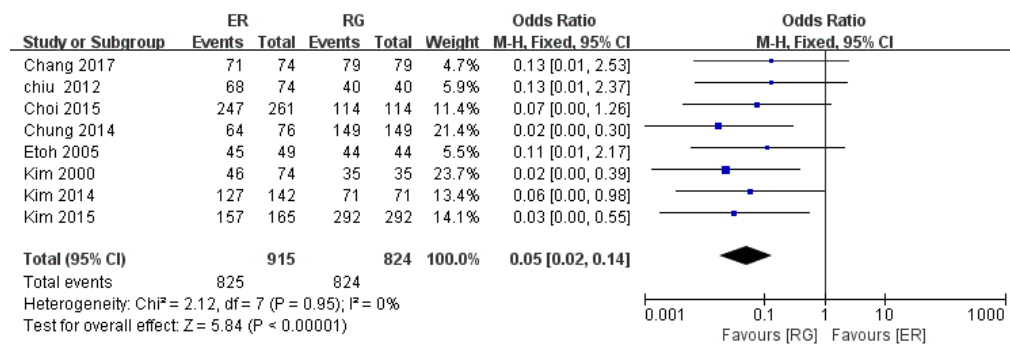
Fig. 4. Forest plot of en bloc resection in the ER group compared with the RG group.

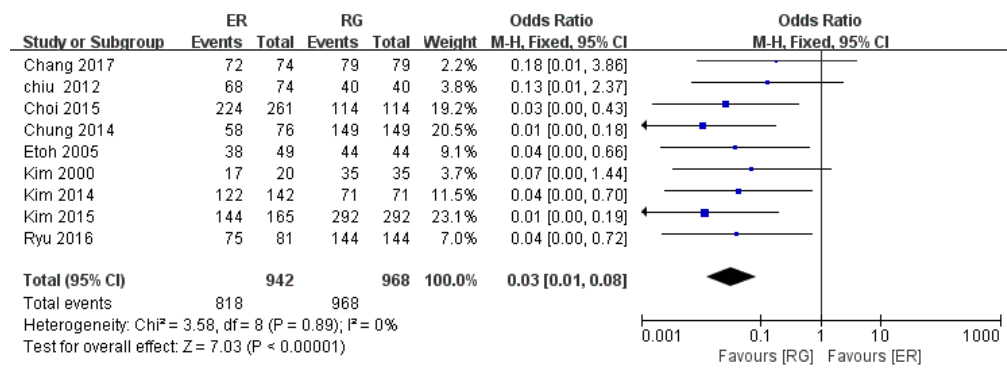
Fig. 5. Forest plot of histological complete resection in the ER group compared with the RG group.

Fig. 6. Forest plot of the number of patient deaths in three years in the ER group compared with the RG group.

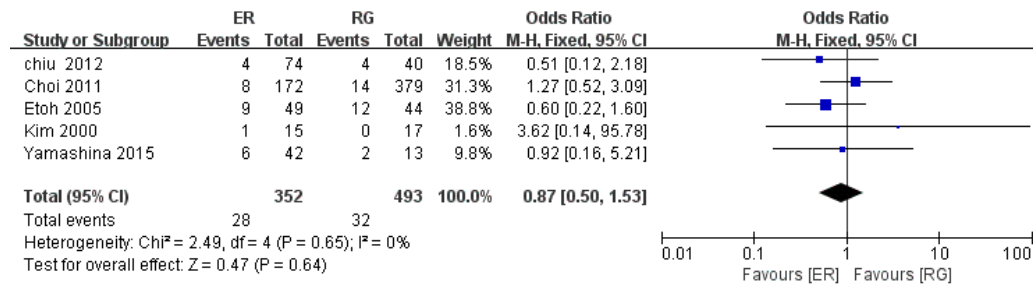


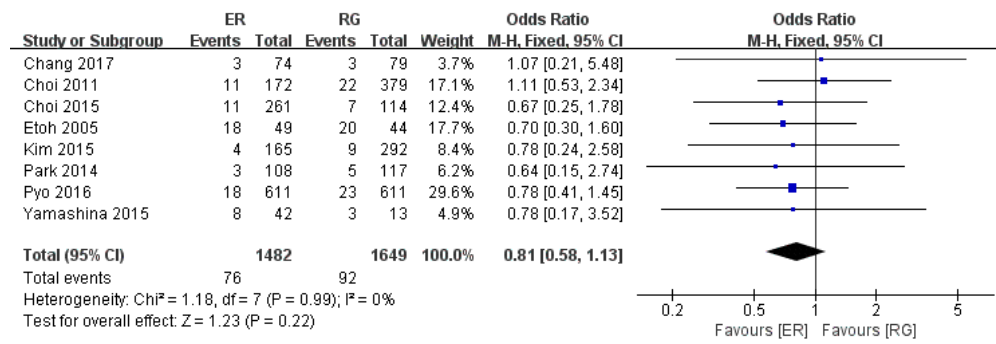
Fig. 7. Forest plot of number of patient deaths in five years in the ER group compared with the RG group.

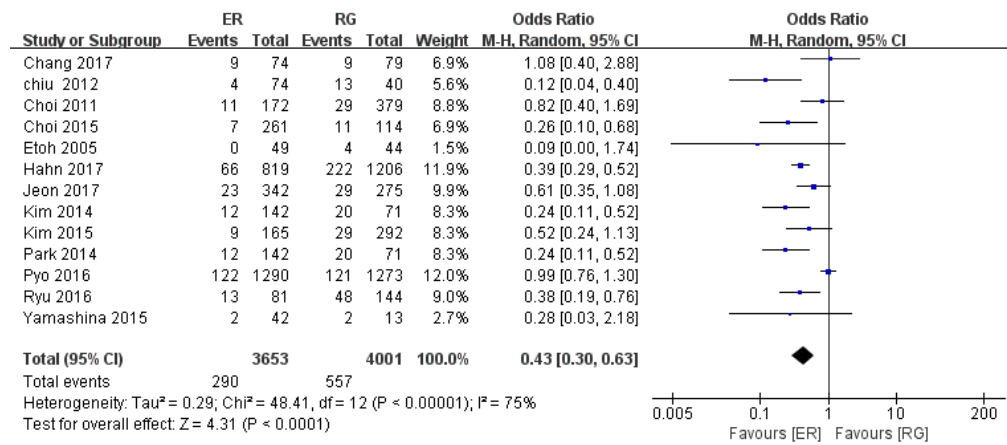
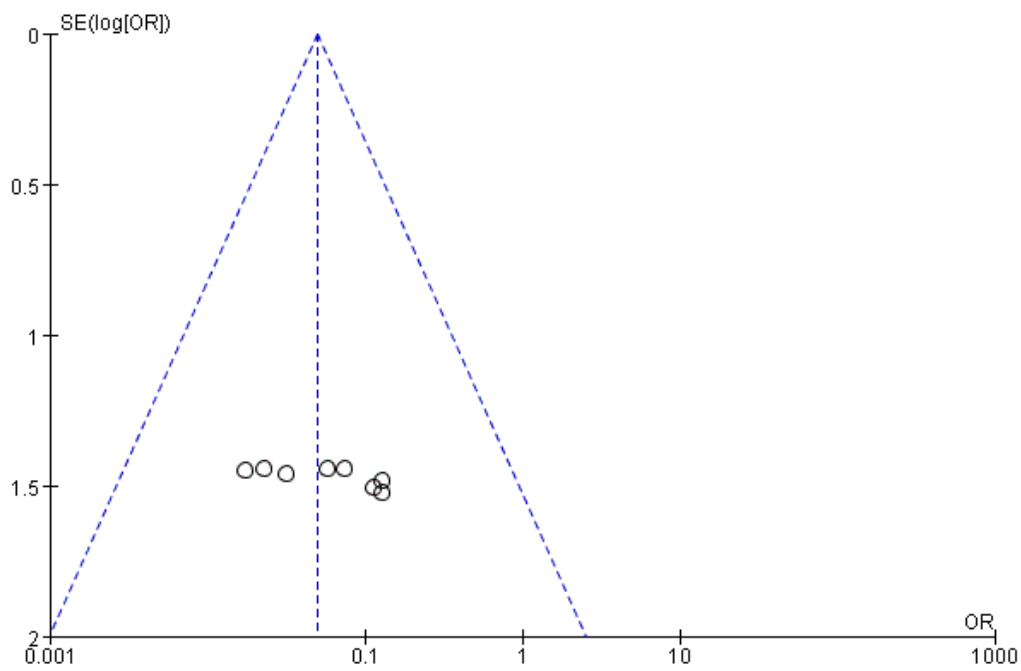
Fig. 8. Forest plot of the complication rate in the ER group compared with the RG group.

Fig. 9. Funnel plot of en bloc resection.

Highlights

1. Radical gastrectomy as a standard treatment for EGC.
2. The feasibility of ER for EGC in Asian patients has not been conclusively determined.
3. This reviews aims to compare the efficacy and safety of endoscopic resection and radical gastrectomy for early gastric cancer in Asia.
4. ER is a good choice for patients with small EGC lesions without lymph node metastasis